REMARKS

Claims

The claims as previously amended are presented above for the Examiner's convenience, and no further amendments have been made herein. The claims currently pending in this Application, therefore, are claims 21-24, 27, 28 and 31-34, wherein claims 27 and 28 are the independent claims with all other claims being dependent thereon.

Priority

As noted in the April 3, 2009 response, prior Examiner Nathan acknowledged the priority claim in paragraph 12 of the Office Action Summary of the October 3, 2008 Action, and checked box "a) All", but did not checked one of boxes 1, 2 or 3 acknowledging *what* was received. The image file of the PAIR database for this application contains a certified copy of both UK priority documents, which had been received as of September 25, 2006, and it is presumed that these certified copies were received in this National Stage application from the International Bureau. Therefore it would be appreciated if the present Examiner could complete the formal acknowledgement that these certified copies have been received.

Examiner's Response to Applicant's Arguments

It is noted with appreciation that in numbered paragraphs **3** and **4** of the Action, the prior rejection under section 103(a) based on Lee in view of Hilberg, and the prior rejection based on Lee in view of Hilberg in further view of Lane, have been overcome in view of Applicant's argument that Hilberg does not qualify as a prior art reference.

However, the Examiner's statement in numbered paragraph **5** of the Action is not understood insofar as it says that Applicant's arguments against the obviousness-type double patenting rejection of claims 29 and 30 "are not found persuasive" but that the rejection has been overcome by cancellation of claims 29 and 30. Since claims 29 and 30 are no longer pending in this application it will be assumed that nothing further need by done by Applicant with respect to the previous rejection of these claims. It is also noted in paragraph **5** that the obviousness-type double patenting rejection over Application 10/563440 has been withdrawn -- it is presumed in view of Applicant pointing out in the April 3, 2009 response that Application 10/563440 had been abandoned.

In paragraphs **6** and **7** of the Action the Examiner states that "Applicants arguments filed 04/03/2009 regarding the rejection of claims 21-24, 27, 28 and 31-34 made by the Examiner under nonstatutory obviousness type double patenting have been fully considered but they are not found persuasive," and that this rejection is maintained for reasons of record in the October 3, 2008 Action.

The Examiner's statement in paragraph **6**, that "Applicants arguments ... have been fully considered but they are not found persuasive," is not understood. Applicant made no argument, but only correctly pointed out that other than Application No. 10/563,440 (which had been abandoned), "these applications all remain pending with no claim allowed" and that "therefore this obviousness-type double patenting rejection remains provisional." It seems that Applicant and the Examiner are in complete agreement, that these obviousness-type double patenting rejections remain provisional (see Examiner's statement to this effect in paragraphs **9** and **11** of the current Action). Moreover, it is understood that the Examiner agrees that the obviousness-type double patenting rejection over *abandoned* Application No. 10/563,440 should be withdrawn (see last sentence of paragraph **5** of the current Action). It is therefore respectfully requested that the Examiner clarify what aspect of Applicant's "arguments filed 04/03/2009" with respect to this obviousness type double patenting rejection were "not found persuasive" so that Applicant can further respond (if necessary).

In paragraphs **8** and **9** of the Action the Examiner states:

> **8**. In regards to the double patenting rejection rejection [sic], Applicant asserts the following:
>
> **A)** No claims have been allowed in any case, thus the rejection should be withdrawn.
>
> **9**. In response to A, this is not found persuasive. The rejection is provisional, as was stated in the previous office action meaning that the rejection was made knowing that claims involved in the rejection have not been allowed. Applicants argument is not persuasive.

However, Applicant *made no such assertion* anywhere in the April 3, 2009 response -- Applicant *has not* asserted that this *"rejection should be withdrawn."* Rather, in the discussion of the obviousness-type double patenting rejections on page 5 of that April 3 response, Applicant correctly noted that because all the cited applications "remain pending with no claim allowed,"

that "this obviousness-type double patenting rejection remains provisional." Applicant concluded, therefore, that "Applicant need not, and in fact cannot respond to this ground for rejection unless and until claims are allowed in the reference applications before allowance of the present application."

Therefore it is respectfully requested that the Examiner clarify the source of the purported "assertion" by Applicant that "**A)** No claims have been allowed in any case, *thus the rejection should be withdrawn*" (emphasis added) or otherwise clarify this statement so that Applicant can further respond (if necessary).

Maintained Rejections, of Record

Double Patenting Rejection

In paragraph **10** of the current Action, the Examiner states that "Claims 21-24 and 27-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 10/563439; 10563,440; 10/594,233; 10/594,234; 11/663,912 in view of Lee (US Pub No. 2002/0002162; Pub.Date Jan.3,2002)." (Action at page 4).

While the Examiner has verbatim repeated the rejection as stated in the previous Action of October 3, 2008, the Examiner has apparently overlooked that the rejection of claims 29-30 has been overcome because these claims have been cancelled, and that the rejection based on Application No. 10/563,440 has specifically been withdrawn (see paragraph **5** of the present Action). Under the circumstances, it must be presumed that the inclusion of claims 29-30 and the rejection over Application No. 10/563,440 was an oversight, and was not a reinstatement of these rejections.

The Examiner's attention is also called to the circumstance that Application No. 11/663,912 cited in the above obviousness-type double patenting rejection has been abandoned and continued as new Application No. 12/408,833, the details of which are reported on the updated table of potentially related applications presented at the end of this response.

As to the remaining obviousness-type double patenting rejections, these rejections remain provisional since no claim has been allowed in any of the reference applications. Applicant thus again notes that, while Applicant does not agree with the Examiner's argument of obviousness-type double patenting, in particular with respect to the application of the Lee reference to this

rejection, Applicant need not, and in fact cannot respond to this ground for rejection unless and until claims are allowed in the reference applications before allowance of the present application.

New Rejections

Claim Rejections - 35 USC § 103

In paragraph **14** of the Action, claims 21, 23, 24, 27, 28 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stokes et al. WO 00/47212, published 08/17/2000, which is equivalent to US 7,074,800 (hereinafter "**Stokes**"). The Examiner asserts that Stokes is directed to quinazoline derivates as angiogenesis inhibitors, and teaches the AZD2171 component of the presently claimed combination therapy at page 57, line 31. The Examiner further asserts in paragraph **15** of the Action:

> The method of treating angiogenesis with the compound of note as well as simultaneously administering radiotherapy and antineoplastic agents such as platinum derivatives like cisplatin and carboplatin (see page 85). It's taught that the radiotherapy and antineoplastic agents may be administered simultaneously, sequentially or separately from administration of the quinazoline derivative (see page 85, lines 1-5). The types of cancers treated by the compounds of Stokes include Kaposi's sarcoma as well as solid tumors such as colorectal and lung cancer (see page 86, lines 11-23).

However, the Examiner then notes in paragraph **16** that "Stokes fails to specifically teach using said compound in a method of treating cancer," and asserts in paragraph **17** that:

> Regardless, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Stokes with a reasonable expectation for success in arriving at a method of treating cancer in a method of administering AZD2171 before after or simultaneously with a platinum anti-tumor agent and radiotherapy. Although stoke fails to specifically use the instantly claimed compound in a method of cancer treatment, any person of ordinary skill could have readily identified said compound for use in a method with a reasonable expectation for success in treating the condition. The reference teaches that AZD2171 is a more preferred compound for use in such treatments. Thus, it would not have been innovative to pick a compound that had been suggested for cancer treatment as the currently claimed method does because such method would have been a product of ordinary skill and common sense as any ordinary person would have been capable of n reading and utilizing the information presented by Stokes. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

Paragraphs **16** and **17** have been quoted in their entirety to avoid mischaracterizing this rejection in that it is not entirely clear what the Examiner is intending to say, *e.g.*, with the statement in paragraph **16** that "Stokes fails to specifically teach using said compound in a method of treating cancer," and the statement in paragraph **17** that "[a]lthough stoke fails to specifically use the instantly claimed compound in a method of cancer treatment ..." To the extent the Examiner intends the terms "said compound" and "the instantly claimed compound" to specifically refer to AZD2171 *per se*, it is noted that Stokes discloses that the quinazoline derivatives of generic formula I, including the many specific compounds that are disclosed and/or exemplified (including AZD2171), are useful in the production of an antiangiogenic and/or vascular permeability reducing effect; and also that compounds of formula (I) are useful in the treatment of cancer, including a cancer involving solid tumors (see page 3, line 1 to page 9, line 23 and Example 240 of Stokes).

Stokes also provides some general teaching on the possibility of administering the compounds of formula I in combination with one or more other substances and/or treatments such as surgery, radiotherapy or a selection from a long list of chemotherapy extending from page 84, line 30 to page 86, line 10 of Stokes. This long list of therapeutic chemotherapy agents includes platinum derivatives such as cisplatin and carboplatin (see page 85, lines 29 and 30 of Stokes). Stokes also mentions solid tumours as disease states that may be treated with the compounds of formula I (see page 86, lines 11 to 23 of Stokes).

However, there is *no disclosure* in Stokes of AZD2171 in combination with a platinum chemotherapeutic agent. Moreover, it is respectfully submitted that there is *no suggestion or any other motivation* in Stokes that might lead the person of ordinary skill to specifically select AZD2171 from among the disclosed antiangiogenic compounds *and* to specifically select a platinum agent from the long list of chemotherapeutic agents *and* to administer the two agents in the combination therapy as presently claimed.

No preference is expressed in Stokes for any particular antiangiogenic and/or vascular permeability reducing agent *to use in such a combination therapy*, and the *only* preference with respect to the *other* agent of such a combination is at page 86, lines 7-10, noting a combination of the vascular targeting agent N-acetylcolchinol-O-phosphate (which clearly is not a platinum anti-tumour agent) with "a compound of formula I as defined hereinbefore." It is respectfully

submitted that there is nothing in the disclosure of Stokes, *when considered as a whole*, that would lead the skilled person to specifically select a platinum anti-tumour agent, no less oxaliplatin, cisplatin or carboplatin, out of the enormous listing of possibilities, and then specifically select AZD2171 out of the broad generic teachings and hundreds of examples of Stokes' compounds, to use it in a combination therapy with the platinum anti-tumour agent. When considering a prior art reference, it is required to consider the reference *as a whole* and not just select out isolated disclosures for combination. It is respectfully submitted that the Examiner could *only* have put together this rejection by impermissible use of hindsight, when selecting and assembling from Stokes the particular components needed to assert that the presently claimed combination therapy is *prima facie* obvious.

Neither Seibert nor Oncology Channel adds anything material to Stokes that would provide any guidance to the skilled person toward making *the particular selections required* for the presently claimed combination therapy.

Seibert discloses the use of cyclooxygenase-2-inhibitors or derivatives thereof in preventing and treating neoplasia, including cancerous tumors (see column 1, lines 6 to 9, column 2, lines 10 to 15 and 41 to 64 of Seibert). Seibert also teaches that the cyclooxygenase-2-inhibitors may be used in drug combination therapy with other antineoplastic agents and provides a long list of such agents (see column 12, line 49 to column 15, line 7 of Seibert). This lengthy list includes several platinum agents, for example carboplatin, cisplatin and oxaliplatin (see column 13, lines 21, 22 and 31 of Seibert).

It is understood that the Examiner has cited Seibert simply to show that oxaliplatin is a known anti-tumour agent, which Applicant does not dispute. However, Seibert fails to provide any teaching that might suggest the presently claimed combination therapy of AZD2171 and a platinum anti-tumor agent, and thus does nothing to fill this fundamental deficiency in the Stokes disclosure.

With respect to the Oncology Channel reference, the undersigned takes exception to the disclosure of such an internet-derived document, having no certain date, being cited as prior art. The reference bears a copyright date *range* of 1998-2009, with a notation on the last page thereof that "this page last modified: 16 Mar 2009." There is no way of knowing *what* was modified on that date or on any date prior thereto but subsequent to the 2004 priority dates to which the

present application is entitled. In particular, there is no way of knowing from the reference whether the disclosure relied upon by the Examiner was present in this document as of Applicant's priority date, and thus whether it is in fact "prior" art with respect to that disclosure.

Nevertheless, it is not seen that this reference adds anything that might suggest a combination therapy of AZD2171 and a platinum anti-tumour agent, and thus does not fill this fundamental gap in the Stokes disclosure. This Oncology Channel reference seems to simply provide a review of different types of lung cancer and includes a section on non-small cell lung cancer. This document provides no teaching in relation to the use of AZD2171 to treat any lung cancer, let alone in relation to the use of a combination of AZD2171 and a platinum anti-tumour agent to treat lung cancer. Thus, again the Oncology Channel reference, even if prior art, fails to supplement the fundamental teaching that is missing from Stokes, that is, it does not suggest the presently claimed combination therapy of AZD2171 and a platinum anti-tumour agent.

It is respectfully submitted that the Stokes disclosure (alone or considered with Siebert or Oncology Channel) does not meet even the minimum criteria for "obvious to try" under *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385, 1398](2007).

The Court in *KSR* explained that the Federal Circuit's "teaching, suggestion or motivation" test provides helpful insight into the obviousness question as long as it is not applied rigidly and that, accordingly, it remains necessary for the Examiner to *identify some reason* that would have led a chemist to modify the prior art in a particular manner to establish *prima facie* obviousness of the claimed invention. Moreover, "obvious to try" does not arise simply because the components of the claimed invention are separately known in the art, but rather a particular combination might be obvious to try only when "there is a design need or market pressure to solve a problem and there are *a finite number of identified, predictable solutions*, and a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."

The Supreme Court's *KSR* reasoning was summarized and applied by the Federal Circuit, for example, in its very recent decision in *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, 90 USPQ2d 1947, 1949-50 (Fed. Cir. 2009). After noting that the obviousness determination turns on the four underlying Graham v. John Deere factual inquiries, the Court continued:

> The Supreme Court has explained that *the Federal Circuit's "teaching, suggestion or motivation" test provides helpful insight into the obviousness question as long as it is not applied rigidly*. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 127 S. Ct. 1727, 1741 [82 USPQ2d 1385] (2007). Accordingly, under KSR, "*it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*" Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 [83 USPQ2d 1169] (Fed. Cir. 2007).

(90 USPQ2d at 1949-50; emphasis added). The Court continued:

> When a person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 127 S. Ct. at 1742. So too, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *Id.* at 1741. *In other cases,* though, researchers can only "vary all parameters or *try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.*" *In re O'Farrell*, 853 F.2d 894, 903 [7 USPQ2d 1673] (Fed. Cir. 1988). In such cases, "*courts should not succumb to hindsight claims of obviousness*." *In re Kubin*, 561 F.3d 1351, No. 2008-1184, slip op. at 14 [90 USPQ2d 1417] (Fed. Cir. Apr. 3, 2009).

(90 USPQ2d at 1952; emphasis added),

It is respectfully submitted that Stokes does not give the skilled person a finite number of identified, predictable solutions to a problem, and certainly gives no guidance or motivation to combine AZD2171 with a platinum anti-tumour agent. Accordingly, even under *KSR* and its low "obvious to try" threshold, the Examiner has not made out a case for *prima facie* obviousness of the presently claimed invention, as the Federal Circuit has interpreted and applied *KSR* to pharmaceutical inventions. Moreover, as discussed above, the disclosures of Seibert and/or Oncology Channel provide no guidance or motivation whatsoever to combine AZD2171 with a platinum anti-tumour agent and thus do not in any way fill this fundamental gap in the Stokes' disclosure.

Accordingly, since the Examiner has not established a case of *prima facie* obviousness, it is respectfully requested that these obviousness grounds for rejection be withdrawn.

Technically Related Pending Applications of Applicant's Assignee

The Examiner's attention is called to the following *updated* Table of pending U.S. applications of Applicant's assignee which might be considered technically related, each of which claims a combination of AZD2171 with another therapeutic agent identified under the heading "Combination." The current status of each application as reported in the PAIR database is given in the right-hand column. Each of the published US applications and PCT applications that are in bold on the below table are listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of each such bold listed published PCT application is provided with the Information Disclosure Statement. All other documents have been previously listed and copies provided in this application.

It is assumed that the Examiner has ready electronic access to each of the pending US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

U.S. Serial No. Filing Date	**First Named Inventor**	**U.S. Pub. No. U.S. Pub. Date**	**PCT Pub. No. PCT Pub. Date**	**Combination With**	**Current Status**
10/240,413 October 1, 2002	Jon Curwen et al.	US 20030144298 July 31, 2003	WO 01/74360 October 11, 2001	Anti-hypertensive	Assigned to Examiner Charlesworth E. Rae in GAU 1611; Non Final Action Mailed 06-29-2009
10/555,389 November 3, 2005	Jon Curwen et al.	US 20060223815 October 5, 2006	WO 2004/098604 November 18, 2004	Anti-angiogenic agent + src inhibitor	Assigned to Examiner Christopher R. Stone in GAU 1614; Final Rejection Mailed 04-29-2009
12/568,643 September 28, 2009	Jon Curwen et al.		WO 2004/098604 November 18, 2004	Anti-angiogenic agent + src inhibitor	Application Undergoing Preexam Processing
10/563,440 January 5, 2006	Stephen Wedge	US 20060160775 July 20, 2006	WO 2005/004871 January 20, 2005	ZD6126	Abandoned
10/563,439 January 5, 2006	Stephen Wedge	US 20060167024 July 27, 2006	WO 2005/004872 January 20, 2005	ZD1839	Assigned to Examiner Benjamin J Packard in GAU 1612; Final Rejection Mailed 06-09-2009

U.S. Serial No. Filing Date	First Named Inventor	U.S. Pub. No. U.S. Pub. Date	PCT Pub. No. PCT Pub. Date	Combination With	Current Status
12/555,592 September 8, 2009	Stephen Wedge		WO 2005/004872 January 20, 2005	ZD1839	Application Undergoing Preexam Processing
10/594,233 September 25, 2006	Stephen Wedge	US 20080125447 May 29, 2008	WO 2005/092303 October 6, 2005	CPT-11 and/or 5-FU	Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Response to Non-Final Office Action Entered and Forwarded to Examiner
10/594,234 September 25, 2006	Stephen Wedge	US 20070135462 June 14, 2007	WO 2005/092385 October 6, 2005	Taxane. optionally IR	Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Non Final Action Mailed 04-30-2009
11/663,912 March 27, 2007	Stephen Wedge	US 20080015205 January 17, 2008	WO 2006/035203 April 6, 2006	Imatinib [Gleevec]	Abandoned
12/408,833 March 23, 2009	Stephen Wedge		WO 2006/035203 April 6, 2006	Imatinib [Gleevec]	Assigned to Examiner James D. Anderson in GAU 1614; Ready for Examination
11/994,824 August 15, 2008	Stephen Wedge	**US 20090176731** July 9, 2009	WO 2007/003933 January 11, 2007	Gemcitabane [Gemzar]	Assigned to Examiner Anna Pagonakis in GAU 1628; Restriction Requirement Mailed 09-30-2009
12/158,266 June 19, 2008	Stephen Wedge	US 20080306094 December 11, 2008	WO 2007/071970 June 28, 2007	pemetrexed	Assigned to Examiner Anna Pagonakis in GAU 1628; Non Final Action Mailed 06-16-2009
12/097,384 June 13, 2008	David Blakey et al.	**US 20090123474** May 14, 2009	WO 2007/068895 June 21, 2007	Angiopoietin-2 antagonist and antagonist of VEGF-A, and/or KDR, and/or Flt1	Assigned to Examiner Phuong N Huynh in GAU 1644; Ready for Examination
12/595,746 October 13, 2009	Stephen Wedge		**WO 2008/125820** October 23, 2008	MEK Inhibitors	Application Undergoing Preexam Processing

The Examiner's Attention is also called to the following *updated* Table of a pending U.S. application of Applicant's assignee which may be considered technically related, which claims a combination of a platinum anti-tumour agent with another therapeutic agent identified under the heading "Combination." The current status of this application as reported in the PAIR database is given in the right-hand column. The published US applications and PCT application

were previously cited in this application and a copy of the published PCT application was previously provided.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

U.S. Serial No. Filing Date	First Named Inventor	U.S. Pub. No. U.S. Pub. Date	PCT Pub. No. PCT Pub. Date	Combination With	Current Status
10/563,668 January 6, 2006	Stephen Wedge	US 20060167027 July 27, 2006	WO 2005/004870 January 20, 2005	ZD6474	Pending before Examiner Savitha M. Rao in GAU 1614; Notice of Appeal Filed 06-24-2009

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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Date: October 14, 2009 By: /Donald Bird/

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